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2004 consensus statements on the management of ovarian cancer: final document of the 3rd International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference (GCIG OCCC 2004)

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Gynecological Cancer Intergroup (GCIG) and its member organizations: [1]AGO-OVAR (Germany), [2]ANZGOG (Australia – New Zealand), [4]EORTC (Europe), [6]GEICO (Spain), [9]GINECO (France), [3]GOG (USA), [8]JGOG (Japan), [10]MRC/NCRI (UK), [7]NCIC-CTG (Canada), [15]NCI-US (USA), [5]NSGO (Scandinavia), [12]RTOG (USA), [11]SGCTG (Scotland), and with representation of [14]IGCS and [13]the organizational team of the two prior International OCCC

International evidence-based consensus statements are important in order to define and update standards of care and to serve not only as guidelines to communities worldwide, but also to provide a rational basis for future research. Two previous successful international ovarian cancer consensus conferences (OCCC) were held in Elsinore, Denmark in 1993 [1] and 5 years later in Bergen aan Zee, The Netherlands [2], where consensus statements were developed on a number of issues including biological and prognostic factors, best current therapy, both surgical and medical, and directions for future research in advanced disease. Since then, international cooperation has become more extensive and intergroup studies are now common as a mechanism to conduct large randomized clinical trials. The Gynecological Cancer Intergroup (GCIG) now constitutes 13 national and international cooperative member groups and governmental organizations [3]. In 2002, the GCIG's general assembly voted to plan the 3rd International OCCC with a more formal process to achieve consensus among the study groups on methodology and standard requirements for clinical trials so as to guide other national and international study groups working in gynecologic oncology. It was anticipated that the OCCC statements would also guide the general medical community and support the pharmaceutical industry in developing appropriate strategies to improve the outcome of women with this disease.

Methodology

Planning committee and agenda

The GCIG is a cooperative organization (http://ctep.cancer.gov/resources/gcig) that includes representatives from four continents and most worldwide study groups performing trials in gynecologic oncology. The general assembly asked AGO-OVAR to be the host organization and formed a planning committee (PC) for the 3rd International OCCC including representatives of seven study groups from three continents: A.d.B. (chair PC, AGO-OVAR), J.P. (chair-elect GCIG, AGO-OVAR), M.Q. (ANZGOG), J.V. (past-chair GCIG, EORTC), T.T. (GOG), M.B. (GOG), M.P. (MRC/NCRI), G.S. (NCIC-CTG), E.A.-L. (chair GCIG, NSGO) and GCIG-secretary Monica Bacon (NCIC-CTG). The PC developed a proposal for the agenda which was approved by the GCIG assembly (first level of consensus) as including three core areas: (A) standard therapy and standard requirements for clinical trials in ovarian cancer; (B) study methodology; and (C) new treatment options and novel approaches. These three basic areas were covered by 12 questions considered as most relevant to direct future clinical and laboratory research via the GCIG's member study groups. Furthermore, GCIG agreed on the agenda, timetable and implementation of a semi-structured consensus process (see below).

The PC chair was delegated to develop funding plans, hire organizational help and select the venue of the meeting.

Selection of participants

The purpose of this meeting was not only to utilize the extensive expertise available through the GCIG, but also to develop a structured consensus process that would allow intellectual participation by all study groups worldwide, thereby ensuring that the eventual recommendations would have broad international acceptance. The GCIG covers four continents with membership of 13 national or international cooperative study groups and governmental/semi-governmental organizations. Each GCIG member organization was asked to provide a list of expert delegates who were regarded as being the most experienced and competent representatives. The number of delegates per organization varied from one to six and reflected the groups attributes (e.g. member institutions, population represented, history of completed

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clinical trials). European groups sent proportionately fewer participants per group to ensure appropriate balance. Asia, however, remained underrepresented and no African group could be identified. In addition, one representative of the International Gynecological Cancer Society (IGCS) and the organizer of the two prior OCCC were invited to participate. Each participant was asked to agree on her/his tasks (see below). If one delegate refused to accept, the respective study group appointed a replacement. Overall, the invitation model resulted in an assembly of 52 experts.

The groups appointed their delegates to one of the three core areas, which were covered by working groups (groups A–C). Each group's delegates were divided into these working groups to guarantee diversity. Each working group was chaired by one responsible chairperson (underlined and *italic*) and two co-chairs (underlined): group A: *T.T. (GOG)*, A.d.B. (AGO-OVAR), G.S. (NCIC-CTG), M.F. (ANZGOG), S.K. (SGCTG), H.K. (MRC/NCRI), G.K. (NSGO), R.M. (GOG), A.P. (GEICO), F.S. (GOG), I.V. (EORTC), K.F. (JGOG), J.P.G. (GINECO), W.M. (AGO-OVAR), B.M. (RTOG), D.P. (NCIC-CTG); group B: *J.V. (EORTC)*, M.B. (GOG), M.P. (MRC/NCRI), E.E. (NCIC-CTG), R.O. (GOG), J.R. (AGO-OVAR), G.R. (MRC/NCRI), S.S. (JGOG), T.H. (NSGO); group C: *M.Q. (ANZGOG)*, E.A.-L. (NSGO), J.P. (AGO-OVAR), M.B. (GOG), D.B. (ANZGOG), S.G. (NSGO), P.H. (MRC/NCRI), E.P.-L. (GINECO), E.T. (NCI-US), P.V. (SGCTG), U.W. (AGO-OVAR), A.C. (EORTC), A.C. (GEICO), S.P. (IGCS), M.R. (GOG).

Gathering of evidence and structured consensus process

One presenter (p) and one discussant (d) were allocated to each of the 12 questions, making 24 p/d and nine chairpersons involved in the preparation of outlines for each question (four in group A, three in group B and five in group C). Again, the p and d for each question came from different groups. The p/d had several months to prepare two comprehensive outlines including all evidence they considered relevant to the appointed question. These outlines were discussed with the chairpersons of each working group and evidence not alluded to was included if appropriate. The modified outlines were then circulated among all members of the respective working group and discussed via e-mail by all participants and further modified before the conference (second level of consensus). The p/d prepared presentations for the conference and all materials were distributed prior to the meeting.

The first day of the 3-day conference was reserved for presentations of the outlines of presenters and discussants followed by a plenary discussion of each question. Through this discussion, working groups were able to gather additional views and evidence. At the end of each discussion a survey of the participants' opinions about the key points was collected to guide the working group activity. On the morning of the second day, working groups separated and discussed each of their questions resulting in agreed first drafts of answers (statements) (third level of consensus). That afternoon, each working group presented their drafts to the auditorium. Each statement was followed by an extensive discussion including comments from each group and suggestions for modifications were gathered for refinement. Again, working groups met separately and refined the statements including the suggestions from the general discussions. Additionally, working groups A and B met and discussed one overlapping issue. Finally, the second drafts of statements were provided that evening (fourth level of consensus).

The third day started with GCIG member study groups meeting separately to discuss their vote on each statement and to elect one voter per group. The consensus process included that each attendee had the opportunity to participate during discussion and in working group sessions, and that at least one member of each member study group commented on each question, but the final vote was limited to one vote per group. Each statement was read in the morning session and each study group commented on refinements required for approval (fifth level of consensus). All refinements per question were then voted on individually until a final statement was reached (majority vote; first level of acceptance). The final statements were considered at the final session and study groups were asked alphabetically whether they agreed or not (final level of acceptance). All 12 statements went through this structured consensus process and each study group commented and voted on each statement. A minority report would be included if one or more study group could not agree on a statement. The level of acceptance was reflected in the voting and is included in the section below.

Finally, the suggestions for a list of unmet needs and topics not included in this conference but important enough to be included in the next OCCC was completed [4]. Each working group had collected proposals for this list during the conference.

Results

12 questions and 12 statements: the 2004 consensus on ovarian cancer

The 12 questions were formally selected from a proposal by the PC and represent those questions regarded by the GCIG assembly as the most important with respect to current standards of care and future clinical trials. The questions and statements are printed in bold and outlined sequentially. The level of acceptance representing the final vote of the 13 member organizations is added to each question in italics. Further explanations were added after the conference and are not printed in bold. All these additions/explanations have been reviewed by all attendees of the GCIG OCCC 2004. Further details including the evidence on which the statements were based are outlined in the three working group documents published together with the statements [5–7].

1. A-1. Is there a need to strictly define the extent and type of surgery for patients in first-line trials?

- **Tissue should be obtained for histopathologic diagnosis to confirm the presence of primary ovarian or peritoneal carcinoma.**
- **Staging should be performed according to FIGO guidelines. For example, this includes at least lymph node sampling and peritoneal staging in early stage invasive disease (FIGO I–IIA).**
- **Up-front maximal surgical effort at cytoreduction with the goal of no residual disease should be undertaken.**
- **When cytoreductive surgery is not possible initially, it should be considered in patients who do not have progressive disease after three to five cycles of chemotherapy.**
- **Patients with ovarian cancer should have their surgery performed by an appropriately trained surgeon with experience in the management of ovarian cancer.**

Level of acceptance: 13/13 (i.e. 13 of 13 GCIG member organizations)

The first bullet point emphasizes that only patients for whom a histological diagnosis is available are included. The second bullet point focuses on the necessity of comprehensive staging, which is of utmost importance, especially in early ovarian cancer. This should include not only the above mentioned examples (lymph node and peritoneal staging) but all surgical procedures necessary to perform comprehensive FIGO staging (e.g. cytology, omentectomy, complete removal of the tumor,

hysterectomy and bilateral salpingo-oophorectomy in patients not suitable for fertility-sparing surgery).

The fourth bullet point focuses on patients who did not receive an appropriate and comprehensive effort at upfront cytoreduction by a trained surgeon (as outlined in third bullet) and who did not progress during chemotherapy. It is not meant that all patients who end up with bulky disease despite an appropriate surgical effort should receive interval debulking. If subsequent referral to a gynecologic oncology unit has taken place, a second surgical procedure prior to initiation of chemotherapy may be considered. The timing of interval debulking surgery should be flexible and the statement only reflects the current most common interval.

2. A-2. What is the impact of post-recurrence/progression treatment on the end points of first-line therapy? Do we need to standardize post-recurrence/progression therapy, or if not, how can we assess its impact on survival?

- **There is an impact of post-recurrence/progression therapy on overall survival (OS).**
- **It is not possible to standardize post-recurrence/progression therapy at the present time.**
- **Although OS is an important end point, progression-free survival (PFS) may be the preferred primary end point for trials assessing the impact of first-line therapy because of the confounding effect of the post-recurrence/progression therapy on OS. When PFS is the primary end point, measures should be taken to protect the validity of analysis of OS.**
- **There should be a clear definition of how to determine PFS.**

Level of acceptance: 13/13

The first bullet point refers to the recent observation that at least one large and two smaller trials have demonstrated a significant difference with respect to OS [5].

The third bullet point stresses the importance that the same schedule for follow-up has to be used in both arms and that the compliance with this schedule has to be assured.

3. A-3. Do we need a common 'GCIG recommended/accepted' standard arm for comparison with any new regimen/approach in first-line trials?

- **There should be a common 'GCIG recommended/accepted' standard arm for comparison with any new regimen/approach. Variations are allowed for clearly defined reasons.**

Level of acceptance: 13/13

4. A-4. Which regimen/kind of regimens can be regarded as standard comparator for future first-line trials?

- **Within a given trial the chemotherapy regimen should be standardized and consistent with respect to drugs, dose and schedule.**
- **The recommended standard comparator for trials of medical treatment in advanced ovarian cancer (FIGO IIB–IV) is carboplatin–paclitaxel.**
- **The recommended regimen is carboplatin with a dose of AUC 5–7.5 and paclitaxel 175 mg/m^2/3 h given every 3 weeks for six courses.**
- **The recommended standard in early stage (FIGO I–IIA) ovarian cancer patients in whom adjuvant chemotherapy is indicated should contain at least carboplatin AUC 5–7.5.**

Level of acceptance: 13/13

The first bullet point stresses that in future trials the regimens should be specified and consistent (e.g. not only 'platinum-based', but specifically which platinum and at what dose).

The last bullet point stresses that a carboplatin dose range is allowed, but that if doses above AUC 6 are considered, it should only be used within combination regimens containing paclitaxel and not as a single agent.

5. B-1. Which patient/disease characteristics should be considered as entry criteria or at least as strata for subgroup analysis in trials?

- **The following patient/disease characteristics should be formally considered for patient entry or as stratification factors: primary site, stage, prior treatment history, histological type, grade, residual disease, measurable or non-measurable disease, serum CA 125, performance status, age and co-morbidity, and other validated prognostic factors. For post-recurrence/progression trials: disease-related symptoms and treatment-free interval.**
- **Before exclusion of any particular patient group the following questions should be considered:**
  - **(a) Is the prognosis of these patients sufficiently different to the group as a whole to conclude without further information that it is inappropriate to include this group of patients?**
  - **(b) Is there good biological, medical or statistical evidence that the treatment is predicted to be considerably more or less effective (or even ineffective) in this group of patients?**
  - **(c) Is the result from the trial likely to be applied to this group of patients?**

Level of acceptance: 13/13

This statement should assist in decision making regarding study design. Taking into account that most study results are generalized for the whole patient population, study groups should ensure exclusion criteria are not too rigorous. Examples for each of these questions are: (a) patients with early ovarian cancer FIGO stage IA grade I most likely will be excluded from chemotherapy trials for ovarian cancer patients at higher risk for relapse; (b) patients whose tumors do not overexpress a specific biologic marker might be excluded from studies evaluating the role of an agent that is expected to work only in patients with tumors that overexpress that specific marker (e.g. HER2neu-negative patients in trastuzumab trials); (c) elderly patients should not be excluded from trials evaluating standard

chemotherapy regimens, because it is very likely that results of this trial will be generalized to this patient population also.

6. B-2. Which kind of phase III randomized study designs can be recommended to the study groups to make future trials quicker, cheaper and more reliable?

- **There is a continuing need to conduct large-scale randomized trials requiring international collaborations through the GCIG.**
- **The primary determinants for whether to use multi-arm or two-arm designs are study objectives, prioritization of the clinical questions and the availability of resources.**
- **When questions to be answered are of similar priority, multi-arm trials may be preferable.**

Level of acceptance: 13/13

7. B-3. Which are the recommended primary end points for future phase II and randomized phase III clinical trials in ovarian cancer? The recommended primary end points for future clinical trials in ovarian cancer are:

- **Phase II Screening for activity: Response* (objective RECIST or GCIG defined CA 125: to be specified in each protocol) (*for non-cytotoxic or biologic agents, other end points such as non-progression, immune response, etc., are being investigated, but are not yet validated).**
- **Phase III**

  Early ovarian cancer: Recurrence-free survival (note: recurrence = recurrent disease + deaths from any cause).

  Advanced first-line: Both PFS and OS are important end points to understand the full impact of any new treatment. Thus, either may be designated as the primary end point. Regardless of which is selected, the study should be powered so both PFS and OS can be appropriately evaluated.

  Maintenance following first-line: OS[1] minority statement

  Post-recurrence/progression trials: The choice of the primary end point needs to be fully justified with appropriate power calculations. Symptom control/quality of life (for early relapse) and OS (for late relapse) may be the preferred primary end points, although PFS should still be used in the assessment of new treatments. Whatever the primary end point, the ability of the study design to detect important differences in survival should be formally addressed.
- **Interim analysis: end points**

Time points for all efficacy analyses should be pre-specified in the protocol.

- **Early stopping/reporting for benefit:**

Primary end point.

If OS is not the primary end point then it is highly recommended that any stopping guidelines include specific criteria for stopping separately for both the primary end point and OS.

- **Early stopping for lack of benefit (in phase III or phase II–III)**

Primary or intermediate end points.

Level of acceptance: 10/13 (for whole statement)

[1]Minority vote by ANZGOG, RTOG, SGCTG: in certain situations PFS can also be considered a primary end point in maintenance trials following first-line therapy.

With the exception of 7. B-3, the level of acceptance was 13/13.

This statement deals with recommendations regarding primary end points for clinical trials. Other end points can be incorporated as secondary end points, and therefore recommendations should not be accepted exclusively. It should be mentioned that the selection of PFS as primary end point mandates rigorous definition of follow-up schedules (see statement 2). OS was regarded the preferable end point in studies evaluating maintenance therapies. However, there was a minority opinion that PFS may also be the primary end point in maintenance therapy trials.

8. C-1. Should maintenance/consolidation treatment be recommended for standard arms in future trials?

- **Current data do not support a recommendation of maintenance/consolidation treatment as a standard arm in future trials.**

Level of acceptance: 13/13

All participants believed that further investigations on the role of maintenance therapy are warranted and, ideally, such maintenance therapy should be compared with an observation arm.

9. C-2. Should dose-intense therapy or intraperitoneal therapy be a standard arm of clinical trials in first-line treatment?

- **There is no role for dose intense therapy with or without hematopoietic support or for intraperitoneal therapy as a standard arm in first-line treatment.**
- **Although there are randomized phase III clinical trials addressing the intraperitoneal route of cisplatin therapy in patients with minimal disease, interpretation of the results remains controversial, and therefore its use has not been widely adopted.**

Level of acceptance: 13/13

The conference believed that further investigations into the role of dose density are warranted. Trials evaluating dose intense therapies or intraperitoneal treatment require design improvement.

10. C3. Are there any subgroups defined by tumor biology who need specific treatment options/trials (and should not be included in 'mainstream trials')?

- **All subgroups of invasive epithelial ovarian cancer should be included in trials until specific studies are available.**

- **Patients with tumors of low malignant potential should not be included in future trials of invasive epithelial ovarian cancer.**

Level of acceptance: 13/13

The conference recognized that as more evidence becomes available, certain histological subtypes might show different biologic behaviors, particularly clear-cell and mucinous cancers. These subtypes may be further defined through molecular characterization. Currently, however, there are insufficient data to exclude any subtypes from trials. Different histological subtypes should be documented within phase III trials to allow subgroup analyses/meta-analyses.

11. C4. How to integrate new treatment modalities into studies?

- **It is currently unclear how to best integrate new treatment modalities into studies; however, identification and validation of predictors of response to new biological agents such as targeted therapies, vaccines and monoclonal antibodies should be a priority in such studies.**
- **Standard clinical end points should continue to be used in phase III studies.**

Level of acceptance: 13/13

The conference was aware of the problems of applying 'old methodology' to 'new approaches', but there was a strong feeling that the optimal use of these new agents is unknown and that it is premature to change study design.

12. C-5. How to integrate translational research in clinical trials in ovarian cancer?

- **Translational research should be considered in the planning of future clinical trials.**
- **Integration requires harmonization of consent processes and standardization of databases, including minimum datasets, and specimen banks, including central pathology review.**
- **Regulatory aspects of shared samples need facilitation.**
- **GCIG trials should have early consultation with GCIG translational research group.**

Level of acceptance: 13/13

The GCIG has gathered a large experience within its translational research and harmonization groups, with the latter having established uniform consent forms and defined regulatory issues associated with sample sharing. Both working groups could offer support if other study groups decide to include translational research in large randomized trials.

Conclusions

The 3rd International OCCC held by the Gynecological Cancer Intergroup in Baden-Baden, Germany, 5–9 September 2004 provided the first worldwide consensus on 12 important questions regarding the standards of care and future research in ovarian cancer. This was the first attempt to integrate a disparate variety of study groups from four continents and to represent each group's view through a structured consensus process. The process was so effective that the level of acceptance was high with unanimous decisions on 11 of 12 statements and only one minority report on a part of statement 7 (Table 1).

It is hoped that this high level of acceptance will help implementation of the consensus statements worldwide. The impact of this consensus conference on future studies will be evaluated in the next OCCC.

Table 1. Votes of each participating group on each consensus statement of the 3rd International Ovarian Cancer Consensus Conference 2004

Study group	Consensus statements											
	1	2	3	4	5	6	7	8	9	10	11	12
AGO-OVAR	y	y	y	y	y	y	y	y	y	y	y	y
ANZGOG	y	y	y	y	y	y	(n)	y	y	y	y	y
EORTC-GCG	y	y	y	y	y	y	y	y	y	y	y	y
GEICO	y	y	y	y	y	y	y	y	y	y	y	y
GINECO	y	y	y	y	y	y	y	y	y	y	y	y
GOG	y	y	y	y	y	y	y	y	y	y	y	y
JGOG	y	y	y	y	y	y	y	y	y	y	y	y
MRC/NCRI	y	y	y	y	y	y	y	y	y	y	y	y
NCI-US	y	y	y	y	y	y	y	y	y	y	y	y
NCIC-CTG	y	y	y	y	y	y	y	y	y	y	y	y
NSGO	y	y	y	y	y	y	y	y	y	y	y	y
RTOG	y	y	y	y	y	y	(n)	y	y	y	y	y
SGCTG	y	y	y	y	y	y	(n)	y	y	y	y	y
Level of acceptance	13/13	13/13	13/13	13/13	13/13	13/13	10/13	13/13	13/13	13/13	13/13	13/13

y, yes/agreed; (n), partial disagreement with minority report.

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